REMARKS

Claims 1, 3-13, and 28 are pending.

The prior rejection of claims 1, 3-6, 8, 9, and 28 under 35 U.S.C. § 103(a) for obviousness over Kooby et al., FASEB J. 13:1325-1334, 1999, in view of Rodgers and McCall, Brit. J. Surg. 87:1142-1155, 2000, has been withdrawn.

Claims 1, 3-9, and 28 are newly rejected under 35 U.S.C. § 102(b) over McAuliffe et al., J. Gastrointest. Surg. 4:580-588, 2000, as evidenced by Alemany et al., U.S. Patent No. 6,403,370. Claims 1, 3-13, and 28 are newly rejected under 35 U.S.C. § 103(a) for obviousness over Alemany, in view of McAuliffe.

Claims 1, 3-6, 8-13, and 28 remain rejected under 35 U.S.C. § 102(e) as being anticipated by Fong et al., US 2002/0071832, and claims 1, 6, and 7 remain rejected under 35 U.S.C. § 103(a) for obviousness over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12:253-265, 2001.

The rejections are addressed as follows.

Rejections over McAuliffe and Alemany

McAuliffe is cited for suggesting the use of oncolytic herpes viruses in the adjuvant setting, where there may be viable tumor cells present in a resection bed, but the tumor burden is low. In this instance, McAuliffe suggests using the relatively attenuated G207, while in the case of palliation for patients with large unresectable tumors, McAuliffe suggests use of NV1020.

As stated by the Examiner, McAuliffe does not teach or suggest the treatment of metastatic cancer. Alemany, however, is cited for teaching that those of skill in the art would

recognize that lysis of tumor cells would generate a systemic antitumoral response that results in the rejection of distant metastases. With respect to claims 4 and 5, which focus on metastases to lymph nodes, the Examiner states "because McAuliffe et al. teach these steps, cancer in the lymphatic system would have been treated. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product."

Applicants respectfully disagree with these rejections, and thus request reconsideration and withdrawal of the rejections. In particular, Applicants note that McAuliffe and Alemany, when discussing treatment of distal tumors, use the systemic immune response to kill cancer cells. This effect is described in more detail by Todo et al. (Human Gene Therapy 10:2741-2755, 1999; a copy is enclosed), who also use the well-known flank mouse model system, subcutaneously inject G207, and describe regression of a remote, established tumor in the brain or in the periphery mediated by the systemic antitumor immune response (abstract). As a strong example of this systemic effect mediated by the immune response, they show that inoculation of G207 causes regression of inoculated tumors, as well as non-inoculated contralateral tumors (p. 2745-2746, bridging paragraph, Fig. 4). To affect not only the local injection site, but also the entire body system, virus amplification (including replication in the infected tumor cells) is necessary (as described in lines 10-12 of the discussion of Todo, at p. 2751). Therefore, at least some tumor cells are necessary, with it being best if all of the tumor cells are present.

This systemic effect is a completely different effect as compared to the one of the present invention, where the injected viruses spread directly to and act at distal sites. In their

experimental examples, McAuliffe injects virus into tumors (see page 582, and the first sentence of the conclusion on page 586) but does not surgically resect the tumor. As a result, the virus was able to produce a burst of viral progeny after infection (Fig. 2, and the second sentence of the conclusion on page 586). The only mention of resection is hypothetical, in the discussion, and includes no mention of treating metastases. Rather, the stated goal of the hypothetical treatment is to "kill residual tumor cells" (page 586, left column).

Alemany surgically debulks the tumor (column 21, line 6), which, as is generally known in the art, is the surgical removal of part of a malignant tumor, which cannot be completely excised, so as to enhance the effectiveness of radiation or chemotherapy of the remaining tumor. Alemany then states that the local tumoricidal effect leads to a systemic antitumoral response that involves rejection of distant metastases" (column 21, lines 17-19).

Alemany thus teaches away from the present invention, in which a tumor is resected for treatment of metastasis of cancer. Further, the systemic effect of Alemany requires virus replication at the site of injection, in tumor cells, to stimulate the immune system to act against metastatic cancer cells elsewhere. In the present invention, such a systemic immune response is not obtained, as the whole tumor is resected, not debulked, prior to application of virus to the tumor bed.

Moreover, and again, McAuliffe does not provide any teaching or suggestion that the virus could reach a distal site of metastasis (or a different organ). In particular, in the model system of McAuliffe, a pancreatic cancer cell line is injected subcutaneously, leading to the development of flank tumors in athymic mice, and this is followed by injection of agents (such as G207) into the flank.

Further, at page 586, last paragraph, McAuliffe names several implications of the study for potential clinical application of oncolytic HSV (i.e., killing residual tumor cells, killing unresectable tumors, and palliation), not including treatment of metastases.

In view of the above, McAuliffe, as evidenced by Alemany, does not anticipate claims 1, 3-9, and 28, and these references also do not render obvious the invention of claims 1, 3-13, and 28. Applicants thus request that these rejections be withdrawn.

Rejection for Anticipation by Fong

The anticipation rejection over Fong et al., US 2002/0071832, has been maintained.

In response to Applicants' prior submission that the inclusion of the mts1 promoter in a long list of promoters does not indicate that Fong envisioned treatment according to the present invention, as well as Fong's own statement to this effect in a declaration, the Examiner responds that nothing in the cited Fong reference specifically indicates a limitation on the type of cancer treated (i.e., that metastases are excluded). Further, the Examiner refers to Alemany as teaching that it was known in the art that oncolytic viruses can be used in the treatment of metastatic cancer, because lysis of cancer cells leads to a systemic immune response. Based on this, the Examiner concludes that an artisan would have recognized that the Fong reference has applications in metastatic cancer treatment.

Applicants respectfully disagree, because the induction of a systemic immune response, as taught by Alemany, is, as discussed above, completely different from the mechanism of the present invention, by which administered virus itself treats metastases, by traveling to sites of metastasis. Further, Applicants submit that the view of Fong, as stated in the above-mentioned

declaration, should be given substantial weight in the determination of this matter, as Fong, in being most likely the person most familiar with this work and an expert in this field, should be persuasive with respect to interpretation of the work.

With respect to Applicants' prior submission that Fong does not teach the treatment of lymphatic metastases, and in reference to claims 4, 5, and 28, the Examiner responds that it is known in the art that the first metastatic cancer detected in cancer patients are tumor cells that spread to lymph nodes. The Examiner further states that any patient with metastatic cancer necessarily has lymphatic metastases, and reiterates that Alemany teaches that administration to resected tumor bed can be used to lyse cancer cells in the bed and such lysed cancer cells can be used to induce a systemic immune response that can treat metastatic cancer.

Applicants again respectfully disagree. First, Applicants note that the cited reference from the Zetter laboratory states that "many," not all, metastases first detected in cancer patients are identified in the lymph nodes. Thus, it is not true that any patient with metastatic cancer "necessarily" has lymphatic metastases, as stated by the Examiner. Further, as stated above, Applicants note that Alemany teaches administration to a debulked tumor, not to a resected tumor bed, from which a tumor has been removed, as is the subject of the present claims. Finally, Applicants again submit that the present claims pertain to the treatment of metastases with an oncolytic virus, not a systemic immune response. In view of these differences, Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1, 6, and 7 remain rejected over Fong, in view of Wong. In response to Applicants' prior submission, the Examiner reiterates that the cited Fong reference does not indicate any limitations on cancers to be treated and that, based on Alemany, the art teaches the

benefits of administering oncolytic virus to resected tumor beds, to lyse any remaining cancer cells and to induce a systemic immune response that targets metastatic cancers.

In response, Applicants submit that, as discussed above, the present invention pertains to the treatment of metastases with administered virus, and not by induction of systemic immunity, as taught by Alemany. Further, as stated above, the interpretation of Fong by Fong himself should be given substantial weight in consideration of this case. Thus, based on the prior declaration of Fong, Applicants submit that the cited Fong reference should not be considered as teaching the treatment of metastases, as indicated by the Examiner. In view of the above, Applicants respectfully request that this rejection be reconsidered and withdrawn.

In the interest of completion, Applicants request that the Examiner consider, in addition to the arguments provided above, submissions made previously in this case. Applicants respectfully submit that, taken together, these submissions make clear that the present invention is both novel and inventive. The prior arguments, which are incorporated herein by reference, are summarized in part as follows.

- The purpose of virus administration in the cited Fong reference is to kill residual cancer cells, in contrast to treating metastases, according to the presently claimed method.
- The inclusion of the mts1 promoter and the different routes/modes of administration in the cited Fong reference were for general exemplary options, but does not mean that Fong should be considered as teaching the treatment of metastases.

- Intravenous administration as noted by Fong and Henderson is carried out so that administered virus reaches tumor sites by the circulatory system, which is different from the administration approach of the present invention.
- Prior to the present invention, there was no teaching or expectation in the art of virus traveling from the site of surgical resection to a distal site, and thus Fong does not provide any suggestion of or motivation for such an approach.
- Express anticipation is not relevant, as Fong does not expressly teach the treatment of metastases at a distal site.
- Inherent anticipation also does not apply, as inherency of a method can only be found if the result always occurs (and thus necessarily flows from the teachings of the prior art), and this is not necessarily the case with the method of Fong, as not all tumors treated according to Fong would have produced metastases, and when carried out in this manner, when metastases do not exist, then the result would not occur. As stated in prior replies, "the fact that a certain result or characteristic may occur... is not sufficient to establish inherency..." M.P.E.P. 2112.
- The patient population treated according to the method of the present invention does not overlap completely with that of Fong.
- Further, even if Fong is interpreted as teaching the genus of treating cancer, Fong does not teach the species of treating metastases, as claimed, and a genus does not anticipate a species.

In view of the above, Applicants request that the rejections in this application be reconsidered and withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Please apply any charges not covered or any credits to Deposit Account No. 03-2095.

Respectfully submitted,

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